# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

Open questions related to adjuvant treatments:

- Role of suppression of ovarian function (some regard this question answered: indirect evidence from trials in the adjuvant and advanced disease settings)
- Role of AI (require ovarian ablation from the very start)
- Role of chemotherapy in addition to endocrine therapies (some would like to avoid the question, especially if higher metastatic potential)
- Duration of GnRH analog suppression, when combined with SERMs

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

## Open questions related to adjuvant treatments:

- Role of suppression of ovarian function (some regard this question answered: indirect evidence from trials in the adjuvant and advanced disease settings)
  - Feasible for study in patients whose ovarian function is maintained because
    1. CT was not given and ovarian function is unchanged
    2. CT was given and ovarian function is either unchanged or resumed
  - Feasible for patients whose physician is convinced that their standard endocrine treatment is tamoxifen alone

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

## Open questions related to adjuvant treatments:

- Role of AI (require ovarian ablation from the very start)
  - Feasible exclusively for those patients who have already suppressed their ovarian function AFTER demonstrated efficient endocrine activity of ovaries
  - Several investigators are convinced that this approach does not require to be compared to SERM-alone control, especially suitable for very young women

Feasible for patients whose physician is convinced they all need ovarian function suppression

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

## Open questions related to adjuvant treatments:

- Role of chemotherapy in addition to endocrine therapies
  - Feasible exclusively for those whose physicians share the doubt on CT being potentially superfluous if „optimal“ endocrine therapy is given
  - The trial may be conducted exclusively if GnRH analog is combined with AI (or SERM)

Feasible for patients whose physician is accepting the doubt about avoiding CT in premenopausal women with breast cancer

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

## Open questions related to adjuvant treatments:

- Duration of GnRH analog suppression, when combined with SERMs
  - Several studies in this population used tamoxifen for 5 years but GnRH analog for various durations (2, 3, or 5 years)
  - Acceptance of ovarian function suppression is a major problem and it is not clear that it should last for more than 2 years

Feasible only for patients who receive a concurrent SERM and cannot be used with AI. Therefore, trial not designed to answer this question

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

SOFT: Suppression of Ovarian Function Trial (IBCSG 24-02)

TEXT: Tamoxifen and Exemestane Trial (IBCSG 25-02)

PERCHE: Premenopausal Endocrine-Responsive Chemotherapy Trial (IBCSG 26–02)

North American Intergroup and Breast International Group (BIG) participation
Coordinating Group: International Breast Cancer Study Group (IBCSG)
Pharmaceutical Partner: Pharmacia

BCSG

# Triptorelin

- GnRH agonist: triptorelin (De-capeptyl depot, Trelstar depot)
- Marketed by Pharmacia in US (pamoate salt) and Ipsen-Biotech in EU (acetate/pamoate salt)
- 28 day depot to be used
- Documented estrogen suppression achieved by the pamoate
- Ipsen pamoate is 99.9% = to Pharmacia pamoate, and Ipsen pamoate is bioequivalent to Ipsen acetate
- Equivalent to Lupron in a randomised clinical trial in patients with advanced prostate cancer (castrate T-levels)
- Ipsen acetate demonstrated an ORR=70% (CR=18%, PR=52%) in a phase II study of patients with advanced breast cancer*

» * Garcia-Giralt et al. Am J Clin. Onc. 1996; 19, 445-458

BCSG

# Tailored Treatment Investigations

## Premenopausal patients with endocrine-responsive disease (ER ≥ 10% and/or PgR ≥ 10%)

The three protocols tailor investigations for two subpopulations:

For patients who remain premenopausal within 6 months after CT, or those for whom tamoxifen alone is considered adequate Rx:
-> SOFT: tamoxifen vs. OFS + tamoxifen vs. OFS + exemestane

For patients who should receive ovarian function suppression from the start:
-> TEXT: OFS +/- CT + tamoxifen vs. OFS +/- CT + exemestane
-> PERCHE: OFS + tam/exe vs. OFS + CT + tam/exe

OFS = ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation. For TEXT, OFS = triptorelin x 5 years, but surgical oophorectomy or ovarian irradiation is allowed after 6 months.

BCSG

# SOFT [IBCSG 24-02, BIG 2-02]

## Patients who remain premenopausal within 6 months after CT or receive tamoxifen alone as adequate treatment

Premeno.

ER ≥ 10% and/or
PgR ≥ 10%

Patients with estradiol ($E_2$) in the premenopausal range either after CT or without CT

Strata

Any CT

No CT

Premenopausal

RANDOMIZE *

**T x 5y**

**OFS + T x 5y**

**OFS + E x 5y**

* Randomization within a 6-month evaluation period after end of CT, or within 12 weeks after definitive surgery for patients with no CT

CT=chemotherapy; T=tamoxifen; E=exemestane; OFS=ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or ovarian irradiation

Target sample size: 3000 patients

BCSG

# TEXT [IBCSG 25-02, BIG 3-02]

## Patients who should receive OFS from the start

Premeno.

ER ≥ 10% and/or PgR ≥ 10%

Candidates to begin GnRH analogue (triptorelin) from the start of adjuvant therapy

Strata**

Any CT

No CT

RANDOMIZE

**GnRH + Tamoxifen* x 5y +/- CT****

**GnRH + Exemestane* x 5y +/- CT****

* to begin at least 6 weeks after start of triptorelin or after CT, whichever is later

** choice of +/- CT may be made by previous randomization in the PERCHE trial.

CT=chemotherapy; GnRH analogue=triptorelin x 5 yrs, but oophorectomy or radiation is allowed after 6 months

Target sample size: 1845 patients

BCSG

# PERCHE [IBCSG 26-02, BIG 4-02]

## Patients who should receive OFS from the start

Premeno.

ER ≥ 10%
and/or
PgR ≥ 10%

Patients for whom CT is considered to be a randomized option (lower risk)

**Strata**

Type of chemo-therapy

Type of OFS

TEXT or T or E


**OFS + TEXT x 5y**
**or T or E x 5y**

**OFS + any CT**
**+ TEXT x 5yr**
**or T or E x 5y**

CT=chemotherapy; OFS=ovarian function suppression using triptorelin x 5 years or surgical oophorectomy or radiation; TEXT=randomized trial comparing tamoxifen vs. exemestane [recommended strata]; T=tamoxifen; E=exemestane

Target sample size: 1750 patients

BCSG